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Filed : December 7, 2001

REMARKS

No amendments have been made to the claims in this response. Claims 1-5, 29-37 and 38-57 are pending in the application, with Claims 1 and 42 being the only independent claims.

Discussion of Rejection under 35 U.S.C. § 112, Written Description

The Examiner has maintained the rejections of Claims 1-5 and 29-36 and 38-57 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner makes various assertions in connection with the written description rejection and dismisses Applicants' prior arguments as unpersuasive. In particular, the Examiner asserts that the "instant specification ... has described only several housekeeping epitopes from seven cancer-related proteins." The Examiner argues that "[t]he specification fails to describe any structural properties that are shared between housekeeping epitopes, only that they are processed by standard proteasomes, not immunoproteasomes." The Examiner also argues that "[b]ecause there is no disclosure of any actual structural difference between housekeeping and immune epitopes, there is no reason to believe that a T cell which binds to a discovered housekeeping epitope cannot also bind an immuno-epitope with a related set of anchor residues."

It appears that the Examiner is stating that the written description requirement is not met unless structural properties defining housekeeping epitopes are disclosed. Respectfully, this is a standard that was not created by the courts or by congress. It is a standard to which other biomolecules, including antibodies, are not held. It is simply not within the power of the Examiner to pronounce a legal test for the present claims when in fact all of the actual legal and policy requirements of the written description requirement have been met.

Applicants remind the Examiner that to satisfy the written description requirement, a patent application must describe the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991). Compliance with the written description requirement of 35 U.S.C. § 112 is essentially a fact-

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based inquiry that will necessarily vary depending on the nature of the invention claimed. *See id.* at 1563 (citing *In re DiLeone*, 436 F.2d 1404, 1405, 168 U.S.P.Q. 592, 593 (CCPA 1971)). A functional description of a material can be sufficient for the written description requirement. *See Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1324 (Fed. Cir. 2002). The Federal Circuit has adopted the standard that "the written description requirement can be met 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics.'" *Id.* (quoting from the Written Description Guidelines, 66 Fed. Reg. at 1106).

As an example, the Federal Circuit in *Enzo* indicated that "the PTO would find compliance with § 112, [first paragraph] for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." *Id.*

In order to give the Examiner abundant clarity as to facts related to the question of whether Applicants have satisfied the written description requirement, Applicants submit herewith the Declaration of Dr. Adrian Ion Bot ("Bot Declaration"). The Bot Declaration establishes certain points of fact, and Applicants provide herein an application of those established facts to the correct legal standard for written description. The Bot Declaration removes these factual issues from the realm of the Examiner's particular opinion as to how to interpret the specification and how it would be interpreted by a person of ordinary skill in the art. These are now established facts, and it only remains for the Examiner to apply these facts to the law, which process Applicants will undertake to assist in this discussion.

Bot Declaration

The following excerpts provide a summary of the key facts established in the Bot Declaration:

3. **FIRST QUESTION:** *Is the group of epitopes that the applicants refer to as "housekeeping epitopes" a meaningful class of epitopes that clearly encompasses some epitopes and excludes other epitopes?*

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3F. It is my opinion as an expert in antigen processing that these common features do indeed define a class of epitopes that is a subset of all epitopes and that can be referred to as housekeeping epitopes, and that the features listed in paragraphs 3B, 3C, and 3D are only all present in housekeeping epitopes. Members of this class are therefore clearly distinguishable from non-members of this class.

4. **SECOND QUESTION:** *What are the defining features of the genus of housekeeping epitopes?*

4B. It is my opinion that these characteristics of the genus of housekeeping epitopes are completely diagnostic of this class of epitopes. I am unaware of the existence of any other factors that would be necessary to further distinguish between housekeeping epitopes and non-housekeeping epitopes.

5. **THIRD QUESTION:** *As a substitute for, or in addition to, the defining features of housekeeping epitopes discussed above, what could be generalized by having a large number of examples of members of this genus?*

5I. For all of the foregoing reasons, it is my opinion that the structure of the class of housekeeping epitopes is best represented and generalized on the basis of the common characteristics of this genus, and that numerous exemplary epitope sequences would not serve to further define the genus. In my opinion and as explained above, there is not a better possible description of a generalizable structure of the members of this genus than the description provided by the applicants in their patent application. Indeed, as with antibodies and other biomolecules as mentioned in subparagraph 5H, it is the biological outcome (cleavage by housekeeping proteasome followed by binding to class I MHC) rather than primary structure that are ultimately more informative for recognizing the member of the genus.

6. In summary of Paragraphs 3, 4, and 5 and their subparagraphs, it is my expert opinion that the class of housekeeping epitopes as defined by the applicants is indeed a true and valid genus with clear members and non-members, and that the description by the applicants of this genus and its structural characteristics is complete and is superior to a description based upon numerous examples of epitope sequences. For the foregoing reasons, it is my expert opinion that the applicants have clearly and sufficiently defined the structural differences between housekeeping epitopes and non-housekeeping epitopes.

7. **FOURTH QUESTION:** *Would a person of ordinary skill in the art of immunology recognize the existence of housekeeping epitopes as a genus, based upon the applicants' description of the invention?*

7D. A person of ordinary skill therefore would recognize the existence of this genus and would appreciate what the genus includes and what it excludes.

8. **FIFTH QUESTION:** *From the disclosure, would a person of ordinary skill in the art conclude that the applicants were in possession of the entire genus of housekeeping epitopes?*

8C. A person of ordinary skill would therefore conclude that the applicants were in possession of the entire genus at the time the description was written.

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9. **SIXTH QUESTION:** *What would a person of ordinary skill in the art understand, as to either of the foregoing questions, if the disclosure instead provided a large number of examples of housekeeping epitopes?*

9C. A large number of exemplary sequences would therefore be far inferior to the applicants' description in permitting a person of ordinary skill in the art to recognize the existence and characteristics of this genus, or to recognize that the applicants were in possession of this genus.

10. In summary of paragraphs 7, 8, and 9, and their subparagraphs, it is my opinion that a person of ordinary skill in the art, reading the disclosure of the above-referenced patent application, would fully recognize the existence and essential characteristics of the genus of housekeeping epitopes, and would recognize that the applicants were in possession of the entire genus at the time the application was filed.

11. **SEVENTH QUESTION:** *Having defined the existence and essential characteristics of the genus of housekeeping epitopes, is the group of T-cells that the applicants refer to as T-cells that "express a T-cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope" a meaningful class of T-cells that clearly encompasses some T-cells and excludes other T-cells?*

11C. As discussed in paragraph 7C, a person of ordinary skill in the art would readily be able to make use of the recited diagnostic features in distinguishing between members and non-members of the genus of housekeeping epitopes. Because a particular T-cell receptor is specific for a particular target, a person of ordinary skill in the art would be able to distinguish the T-cells of the claimed compositions from other T-cells based on the description of housekeeping epitopes provided by the applicants.

As one familiar with the level of ordinary skill, Dr. Bot declares in paragraph 7 that a person of ordinary skill would recognize the existence of the genus of housekeeping epitopes and would appreciate what the genus includes and what it excludes. *Bot Declaration* at paragraph 7. Importantly, Dr. Bot declared that a person of ordinary skill would conclude that the applicants were in possession of the entire genus of housekeeping epitopes at the time the description was written. *Bot Declaration* at paragraph 8.

Satisfaction of the Written Description Standard

Applicants have satisfied the legal standards set forth in the recent Federal Circuit decision in *Enzo*. The written description requirement is satisfied because the specification provides sufficiently detailed, relevant identifying characteristics including partial structure for all housekeeping epitopes, other physical and/or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, and complete sequence structure for several working examples, including one example from tyrosinase.

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A. Partial Structure, Physical and/or Chemical Properties

The specification describes all of the relevant identifying characteristics for all housekeeping epitopes. This fact is established by the Bot Declaration. Dr. Bot declares that one key feature that housekeeping epitopes all share is that they are polypeptide fragments of larger proteins and are formed via activity of the housekeeping proteasome that is predominantly active only in certain cell types under certain conditions. See Bot Declaration at paragraph 3. Specifically, the housekeeping proteasome is predominantly active in peripheral cells, including neoplastic or chronically infected cells, so long as such peripheral cells are not undergoing interferon-induced gene expression. Housekeeping proteasomes are not predominantly active in pAPCs. See *id.* Also, he declares that another key feature that housekeeping epitopes all share is that each has an affinity for at least one allele product of class I major histocompatibility complex (MHC). Further, Dr. Bot declares that another key feature that housekeeping epitopes all share is that they are displayed on the surface of cells in which the housekeeping proteasome is predominantly active. See *id.* The specification provides all of the above-mentioned relevant identifying characteristics for all housekeeping epitopes, which include the partial structure and properties for all housekeeping epitopes. See for example, page 110, lines 1-11; page 22, lines 16-26; page 20, line 29 to page 21, line 1; page 110, line 32- page 111, line 2; and page 41, lines 11-24.

B. Disclosed Correlation Between Function and Structure

Further, there is a disclosed correlation between the structure of the housekeeping epitopes and their function, for example being epitopes that are displayed on a cell in which a housekeeping proteasome is predominantly active. Display on a target cell is dependent upon MHC binding and presentation. MHC I binding capability correlates with the sequence structure of the epitope. The specification explains that the encoded MHC epitopes are preferably 9-10 amino acids in length, and as mentioned above, numerous MHC alleles are known in the art and disclosed in the written description. The housekeeping epitopes are disclosed as having the preferred size for MHC binding and as having amino acid motifs with affinity for class I MHC.

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Thus, the specification discloses a correlation between the function and structure of housekeeping epitopes.

C. Complete Sequence Structure for the Working Example and Disclosure of Representative Number of Species

Consistent with the standard set forth in *Enzo* and as acknowledged in the Office Action, the specification provides an exemplary housekeeping epitope from tyrosinase, FLPWHRLFLL. This working example is representative of all housekeeping epitopes and the disclosure of more species, or a "representative number" as referred to by the Examiner, would not aid in showing possession of the genus. This is because this single example is representative of the entire genus and no additional examples would provide additional generalizable information. The tyrosinase housekeeping epitope is representative in terms of its length of 10 amino acids, its region having MHC binding affinity, it having a proper C-terminus, and it being an epitope produced by a housekeeping proteasome.

Further, there is a disclosed correlation between the structure of the housekeeping epitopes and their function, for example being epitopes that are displayed on a cell in which a housekeeping proteasome is predominantly active. Display on a target cell is dependent upon MHC binding and presentation. MHC I binding capability correlates with the sequence structure of the epitope. The specification explains that the encoded MHC epitopes are preferably 9-10 amino acids in length, and numerous MHC alleles are known in the art and disclosed in the written description. *See Specification* at page 110, lines 1-2. The housekeeping epitopes are disclosed as having the preferred size for MHC binding and as having amino acid motifs with affinity for class I MHC. Thus, the common features are highly correlated with structure. For housekeeping epitopes, function is dependent upon structure, and function is a proxy for the underlying structure from which they are so specifically formed from an antigenic protein. Therefore, the specification discloses a correlation between the function and structure of housekeeping epitopes.

As set forth in the Bot Declaration, numerous specific examples of housekeeping epitopes, providing the sequences of individual epitopes, would not assist further in defining the genus of housekeeping epitopes or in distinguishing between members of this genus and non-members. Bot Declaration at paragraph 5. The genus is best defined as set forth in the

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specification, by the combination of relevant identifying characteristics (functional, structural, and chemical properties) and the working example. *See id.*

Applicants respectfully assert that the disclosure of general common features of this genus, together with the expressly disclosed epitope that exemplifies the common features of the claimed genus, is sufficient to satisfy the written description requirement under the *Written Description Guidelines*. The *Written Description Guidelines* specifically state that one species can be adequate to support a genus. *See Written Description Guidelines* at page 1106. Whether or not a single embodiment is sufficient is determined by the level of skill and knowledge in the art. Factual documentation of how the specification would be read and understood by a person of ordinary skill in the art has been provided in the Bot Declaration and is therefore not a matter on which the Examiner can simply disagree.

D. Response to the Examiner's Arguments

In the Office Action, the Examiner attempts to refute Applicants' prior arguments that written description is satisfied. The Examiner's assertions are based upon factual questions that have now been fully established by the Bot Declaration. In particular, the Examiner argues that the "instant specification ... has described only several housekeeping epitopes from seven cancer-related proteins." The Examiner argues that "[t]he specification fails to describe any structural properties that are shared between housekeeping epitopes, only that they are processed by standard proteasomes, not immunoproteasomes." Furthermore, the Examiner asserts that "there is no disclosure of the enzymes, cofactors and/or chaperonins responsible for the differential processing of housekeeping epitopes."

The Examiner also argues that "T cells which recognize 'housekeeping' epitopes may also recognize 'immuno'-epitopes" and that "there is no disclosure in the specification on how to distinguish the T cells of the claimed composition from other T cells other than the fact that they are able to bind to epitopes produced by standard proteasomes that are not produced by immunoproteasomes." The Examiner continues that "[b]ecause there is no disclosure of any actual structural difference between housekeeping and immune epitopes, there is no reason to believe that a T cell which binds to a discovered housekeeping epitope cannot also bind an immuno-epitope with a related set of anchor residues." The Examiner cites *Fiers v. Revel* (25

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U.S.P.Q.2d 1016 (1993)) for the proposition that adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it.

1. Applicants' Disclosure Adequately Described All Members of the Genus of Housekeeping Epitopes

The specification provides the underlying cellular biology and immunology related to the claimed genus, and all of the relevant identifying characteristics and routine assays for exploiting those characteristics. See Bot Declaration at Paragraph 3, *et seq.* Thus, the specification provides the best possible description of the entire genus of housekeeping epitopes and permits one of ordinary skill in the art to distinguish members of the genus from non-members. The discovery of the significance of the underlying and fundamental cellular immunology conclusively shows Applicants' possession of the entire genus of housekeeping epitopes, clearly conveys that Applicants have invented the subject matter which is claimed, and puts the public in possession of what the Applicants claim as the invention, thus satisfying § 112, first paragraph. See *In re Barker*, 559 F.2d 588, 592 (C.C.P.A. 1992); *M.P.E.P.* § 2163(I) and *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566 (Fed. Cir. 1997).

Disclosure of a large number of species would demonstrate possession of less than the entire genus and is inferior to the disclosure in the specification. Short of disclosing all members of the genus, which is not required and would have been incredibly burdensome, Applicants have provided the best description of the genus.

As explained in the Bot Declaration, disclosure of a large number of species would not assist further in defining the genus of housekeeping epitopes or in distinguishing between members of this genus and non-members. See Bot Declaration at paragraph 5. A large number of species would only provide a large number of primary amino acid sequences. However, as set forth in the Declaration, it is incorrect and simplistic to expect that all relevant structure or characterization information lies only in the primary amino acid sequence of a class of epitopes. *Id.* The contrary is true, there are common characteristic features described in the specification that are shared by all housekeeping epitopes, and these features best define members of this genus.

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Thus, the disclosure of the specification is superior to that requested by the Examiner and puts the public in possession of any housekeeping epitopes.

2. The Relevant Identifying Characteristics Shared Among the Class of Housekeeping Epitopes Disclosed by Applicants Are Highly Correlated with Structure

The Examiner argues that the disclosure of several exemplary epitopes alone does not show possession of the entire genus. Applicants have provided far more than several housekeeping epitopes. Respectfully, disclosure of even a single housekeeping epitope with the disclosure of all of the relevant identifying characteristics of all housekeeping epitopes, demonstrates possession of the entire genus. This is supported by the Bot Declaration at paragraphs 8 and 9.

Moreover, the common features adequately describe the structural properties shared among the class of housekeeping epitopes. *See id.* at paragraph 5E. The common features are highly correlated with structure. For housekeeping epitopes, function is dependent upon structure, and function is a proxy for the underlying structure from which they are so specifically formed from an antigenic protein. *See id.*

3. Analogy to Antibody Art Provides Additional Evidence of the Adequacy of Applicants' Disclosure

There are numerous examples of important types of biomolecules and systems for which functional criteria are employed as proxies for highly complex structural characteristics. *Enzo* and the *Written Description Guidelines and Training Examples* recognize that antibodies may be described functionally based on the general knowledge in the art of antibody structure and specification of the inducing immunogen. Specifically, for antibodies, the written description requirement is satisfied when there exist: (1) a routine method for making the antibody; (2) well-defined structural characteristics for the antibody (although no actual sequences); (3) identified functional characteristics of the antibody; and (4) a technology which was well developed.

Just as in the case of antibodies, Applicants have disclosed the understanding of the underlying science related to differential proteasomal processing and housekeeping epitopes. First, there is a routine and reliable method for (1) making housekeeping epitopes, including

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identifying and distinguishing housekeeping epitopes from non housekeeping epitopes, as referenced more fully above. (2) As discussed above and in the Bot Declaration, there are also well-defined characteristics based upon structure for housekeeping epitopes. (3) The specification discloses functional characteristics and a large number of MHC binding motifs, each of which also acts as a more reliable proxy for structure than would any reasonable number of exemplary amino acid sequences. (4) Finally, the technologies of MHC action and binding, as well as proteasomal processing are both well understood in terms of their application for the instant application. The techniques and assays necessary to make and characterize housekeeping epitopes are well within the ability of the skilled artisan. Therefore, analogy to antibody art provides additional evidence of the adequacy of Applicants' arguments regarding written description. Just as with antibody claims, the instant claims are described in sufficient detail to satisfy the written description requirement.

4. The Proteasomes and Their Different Subunits Are Fully Described in the Application

As for the assertion in the Office Action that there is no disclosure of the enzymes, cofactors and/or chaperonins responsible for the differential processing of housekeeping epitopes, Applicants respectfully disagree. The proteasomes and their different subunits are fully described in the application. Applicants direct the Examiner's attention, for example, to the specification at page 23, line 15 to page 24, line 28 ("Different Proteasomes Yield Different Epitopes"); page 25, line 28 to page 26, line 4; and Figure 2.

5. Applicants' Disclosure Adequately Described How to Distinguish the T cells of the Claimed Compositions from Other T cells

As discussed above, the specification has fully described the genus of housekeeping epitopes in satisfaction of the written description requirements. The specification describes and the claims are drawn to isolated T cells, where each T cell expresses a T cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope. *See for example, specification* at pages 107-108. Furthermore, the specification describes how to test to verify that

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a given T cell expresses a T cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope, which permits one of skill in the art to distinguish members of the claimed genus. A person of ordinary skill in the art would readily be able to make use of the recited diagnostic features to distinguish members of the claimed genus. The Examiner's statement that "there is no reason to believe that a T cell which binds to a discovered housekeeping epitope cannot also bind an immuno-epitope with a related set of anchor residues," ignores the language of the claim requiring that the T cell expresses a T cell receptor specific for an MHC-peptide complex comprising a first housekeeping epitope.

In Summary

As the Bot Declaration establishes, the description in the specification clearly illustrates to the skilled artisan that Applicants were in possession of the claimed subject matter, including the feature of housekeeping epitopes, at the time of filing. As discussed above, the claimed invention has been described in the manner that best shows possession and in a manner that provides the most to the public. The analogy to antibodies provides additional support for these points. Therefore, Applicants respectfully assert that the written description requirement of 35 U.S.C. § 112, paragraph 1, has been satisfied consistent with established case law and the *Written Description Guidelines*. See *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002).

In view of all of the foregoing, Applicants respectfully request withdrawal of all rejections for lack of written description under 35 U.S.C. § 112.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, arguments in support of the patentability of the pending claim set are presented above. In light of the above amendments and remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any

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remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: March 27, 2006

By: Sheila R. Gibson

Sheila R. Gibson
Registration No. 54,120
Attorney of Record
Customer No. 20,995
(619) 235-8550

2477359
032706